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A focus on the history of light microscopy for cell culture

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Introduction

The studies of natural philosophers of the sixteenth and seventeenth century encouraged development and improvement of several instruments, including the air pump, clock, barometer, thermometer, microscope, and telescope. Such instruments, particularly the microscope and telescope, expanded the scope of the human senses, forever changing the relationship between the observed and the observer. This then changed the type of questions asked by natural philosophers, and had an effect on the interpretation of what was observed¹. Whereas prior to the widespread use of the microscope, natural philosophers would conceive their (scientific) knowledge as being deduced from first principles, later scholars (following Isaac Newton, for example) began in a different way – by first observing the phenomena and reducing it to find principles from which the phenomena can be explained (Bristow, 2010). This 'Newtonian'-type method became the preferred process of knowledge creation in the eighteenth century, potentially aided by instruments such as the microscope.

The use of lenses in Europe began with the ancient Greeks and Romans, and there is evidence that the ancient Egyptians also used similar lenses. Persian mathematician and philosopher Ibn-al-Haitham [Alhazen] (c.962-c.1038) produced a treatise on convex lenses and magnification, including how the anatomy of the eye related to vision, that was translated into Latin in the twelfth century. This demonstrates not only an Arabic interest in the use of lenses and functional physiology, but also sufficient similar European interest to justify its translation in the 1100s. Later, Roger Bacon (1214-1292) would also write on the use of various lenses and their properties. For example, Bacon described the use of curved lenses to aid with reading, also drawing on the works of Islamic scholars, including Ibn-al-Haitham and al-Kindi [Alkindus], and Claudius Ptolemy's Arabic translation of *Optics* (see Bacon's *Perspectiva*, part of *Opus Majus*,

¹ This became particularly evident through the eighteenth and nineteenth centuries as 'natural history' became a preferred method, placing emphasis on the observed rather than the observer (Magner, 2002).

sent to Pope Clement IV in 1267). Such practical use led to the thirteenth century development of eyeglasses, likely to have occurred in Italy². The frequency with which eyeglasses are mentioned in the fourteenth century suggests that they were an oft-used, yet still admired, invention. Current Purdue Liberal Arts College History Professor Emerita, Lois Magner, suggests that the invention of eyeglasses must have had a significant effect on fourteenth century attitudes regarding disability and limitations of the human body, since some could now be overcome by the use of human inventions (Magner, 2002, p135). Not only had the relationship between the observed and the observer changed then, but there was also a different conception of bodily limitations during this period. Extension of sight (using microscopes and telescopes) and the improved ability to see (for those with some long- or short-sightedness), demonstrate how human intervention was succeeding in widening the human experience.

Using the example of cell biology and cell culture, this paper will discuss how the microscope was developed and utilised by natural philosophers to, initially, extend what was visible. Once the invisible became the visible, and natural philosophy developed a new branch of 'natural science', rational philosophers started with the observed to deduce principles for explaining their world. Such observations began initially by extrapolating phenomena relatively well understood in the visible world. Generally, Christian scholars in Europe of the eighteenth and nineteenth centuries believed that God had made the human mind able to conceive all of His creations, and therefore microscopy was a legitimate way of knowledge creation. Still produced by those with an understanding of optics and lens manufacture, nineteenth century microscopes were improved and developed for fieldwork. Artefacts could be eradicated, and resolutions increased. Many biologists of the late nineteenth and early twentieth centuries found uses for the microscope beyond the study of natural history. Cell and tissue culture techniques were developed to help scholars learn more about the structure and function of animals and plants. The light microscope became an essential piece of equipment in specialised, institutional laboratories; most cells are invisible to the naked eye, and the light microscope continued to be used in order to make the unobservable observable. Despite debate in the first half of the twentieth century regarding the usefulness of cell and tissue culture, several culture methods were developed and became generally used throughout the biological sciences, since its usefulness became clear for experimental geneticists, cell biologists, medical scientists, and biochemists for example. The development of stains and live cell imaging would eventually allow more to be learned about cell structure and function, an exercise continued today. More recently however, with researchers expected to have applicable knowledge of many techniques and instruments, I suggest that the microscope has become a 'black box' in late-twentieth and early-twenty-first century biological science. The black box theory suggests that there is an input and an output

² Both Friar Alessandro della Spina of Pisa (d. 1313) and nobleman Salvano d'Aramento degli Amati (d. 1317) have been suggested as inventors of eyeglasses, however it is also possible that a glazier may also have been responsible.

of a system, although the exact functions of that system may not be known or understood; this is the 'black box'. The consequences of this could potentially lead to misinterpretation and misuse of data and results, distorting our understanding of the world (either intentionally or unintentionally).

The use of the microscope in early modern natural philosophy

By the sixteenth century, lens manufacture was a well-established industry in Europe, and practitioners had accumulated much empirical knowledge of their trade. The first single lens and compound microscopes (a microscope with two or more convex lenses) were developed around 1595 by Dutch lens-maker Zacharias Janssen (c.1585-c.1630)³. This early compound microscope included both a convex and concave lens at the end of a brass tube. It is possible that Janssen's compatriot and technical innovator Cornelius Drebbel (1572-1633) however was the one who brought the Janssen device to the attention of scholars, demonstrating the compound microscope in London (1619) and Rome (1622). Italian astronomer Galileo Galilei (1564-1642) also created his own version, patented in 1609. Others then developed on the compound microscope concept as it allowed for higher magnification, although this was only probably still around 10-fold. English microscopes of the time were often created from wood and leather, whereas Italian microscopes were generally smaller, and fashioned from wood and brass. Initially, some philosophers were concerned with the scholarly introduction of the microscope, suggesting it misled the senses, whilst others were concerned it was a device associated with witchcraft (Magner, 2002). Generally however, scholars appeared to appreciate the new possibilities the instrument promised. Marcello Malpighi, Robert Hooke, and Antoni van Leeuwenhoek were three particularly distinguished gentlemen who utilised microscopy in the seventeenth century in a way that would not be seen again until the nineteenth century.

Italian physician Marcello Malpighi (1628-1694) made extensive use of microscopy in his studies into anatomy, physiology, embryology and histology. In particular, Malpighi extended seventeenth century knowledge of structure and function of the human body. It is possible that Malpighi became interested in experimental work whilst studying philosophy at the University of Bologna; his method was not appreciated there however, and his approach was subjected to attacks. Possibly in light of this, Malpighi accepted a chair in theoretical medicine, created for him at the University of Pisa in 1656. As well as becoming a member of the Accademia del Cimento [Academy of Experiments], Malpighi corresponded regularly with the Secretary of the Royal Society, Henry Oldenberg, and was elected as a Fellow in 1669; in return, Malpighi promised to become the chief promoter of natural history in Italy, primarily by communicating and collaborating with other researchers in the region. (It was this task that encouraged Malpighi

³ It is possible that the young Zacharias had some help in this project from his father, Hans Janssen.

to move towards more experimental methods.⁴) The Royal Society would also publish two of Malpighi's books (on botany and zoology respectively) in 1675 and 1679. Having arranged for his works to be sent to the Royal Society in the event of his death, the Society also published Malpighi's latter works posthumously. Although relatively limited, Malpighi made the most of his microscopy preparations, by staining samples with ink, and exploring various illumination methods. In addition, Malpighi was a good artist, able to sketch what he saw through his microscopes with relative accuracy, having his own sketches incorporated into his texts published by the Royal Society (Cavazza, 1980).

Robert Hooke (1635-1703) developed his compound microscope in the 1660s, whilst Curator of Experiments at the Royal Society, and Gresham Professor of Geometry at Oxford University. Despite being a leading inventor and instrument designer, Hooke did not make his own microscopes⁵, however contributed to their design. Hooke's was an elegant compound microscope, with a total of four lenses, and an eyepiece lens, and Hooke's study of light enabled him to introduce improvements to the established compound microscopes. As Curator at the Royal Society, Hooke's role was to organise demonstrations at the Society's weekly meetings; this frequently included microscopical demonstrations. Many of these observations were published in Hooke's *Micrographia* (1665). Amongst many items observed and described in *Micrographia* is cork, which is described as comprising "cells" or "little Boxes"; Hooke suggests that this was the first time he had seen (and possibly anyone had seen) such "*microscopical* pores" (Hooke, 1665; original emphasis). Similar observations were reported by Hooke's colleague Nehemiah Grew (1628-1712) and Malpighi, who saw what we now recognise as the plant cellulose wall. Grew, Secretary of the Royal Society from 1677, presented an essay to the Society in 1671, based on his opinion that plants and animals comprised similar structures (since both were designed by "the same Wisdom") (Magner, 2002, p144). At the time, most microscopists would have assumed that all that could be seen under the microscope would have been a creation of God, and that their interpretation of the creations would have been as God intended.

It is unlikely however that Hooke's microscopes would perform as well as Leeuwenhoek's. In 1668, the Dutch textile merchant Antoni van Leeuwenhoek (1632-1723) made a visit to London, interested in Hooke's *Microscopia* and the images of textiles drawn from observations with microscopes; later it appeared that Hooke's work would become the model for Leeuwenhoek's own. Leeuwenhoek created his own microscope, with the sun as his illumination, and his own eyes as the light detectors, describing 'free cells' (cells without cell walls) in 1674, and 'animacules'

⁴ Cavazza suggests that Malpighi's experimental, 'natural science' approach, was favoured by members of the Royal Society in England (Cavazza, 1980; Magner, 2002).

⁵ Hooke's microscopes were probably all made by the London instrument maker Christopher Cock.

in pond water droplets in 1676; the Royal Society were sceptical at first⁶, however Leeuwenhoek's findings were confirmed by (then Fellow of the Royal Society) Hooke⁷. Leeuwenhoek made his own simple microscopes from lenses he would craft himself, which are often described as superior to most other seventeenth century microscopes (see Magner, 2002). For example, Leeuwenhoek developed his skills in creating lenses for his single-lens microscope design, using blown glass for his designs; the example of a Leeuwenhoek microscope at the Utrecht museum has a lens of only one millimetre thickness, but which has a resolution of almost one micron. In order to establish quantitative measurements as far as possible, Leeuwenhoek would compare the size of simple objects with his observations, such as a strand of hair. This was particularly useful for his contemporaries. Leeuwenhoek was made a Fellow of the Royal Society in 1680, and his letter describing the 'animacules' observed in pond water was published in 1683, having been translated by the Royal Society⁸. When he died, Leeuwenhoek bequeathed 26 microscopes and extra lenses to the Royal Society.

For these early microscopists, what they saw under the microscope would be logically explained as an extension of the visual world they already knew (Fournier, 1991), (hence the vocabulary used, such as 'cell' and 'fibre' perhaps). Since God had created man capable of comprehending the world He created (see above), variations on mechanical philosophy allowed scholars to construct their world based on this theory (Leeuwenhoek was typical of this) (Fournier, 1991). It is possible that the scholars of the late seventeenth century actively constructed their views of nature to conform to the vessels and fibres observed via microscopy. For these reasons, it has been suggested that the microscope during the early eighteenth century was not a particular requirement for learning about how the world worked. This could contribute to the lack of knowledge generated regarding the 'cell' for the next hundred years, despite the range of interesting observations made through the seventeenth century. The cell itself was somewhat of a 'black box' during this period. Although individuals such as Hooke and Leeuwenhoek had suggested that 'cells' could be seen with the early light microscopes, little detail (other than the cell membrane or wall, and the nucleus) could have been clearly seen. These early

⁶ Leeuwenhoek was unable to read Latin, which, Magner (2002) suggests, left him free from current existing dogma, and gave him independence. Although he generally presented his observations as fact, he was open-minded enough to consider plausible interpretations of others.

⁷ Magner (2002) suggests that although initially based on the work of Hooke, Leeuwenhoek's observations were superior to his predecessor's. Tests carried out by the Royal Society after Leeuwenhoek's death suggested that whilst Leeuwenhoek's microscopes had magnifying powers of 50- to 200-fold, Hooke's were only 20- to 50-fold. Leeuwenhoek's work were arguably the first live cell imaging studies.

⁸ Eventually, Leeuwenhoek would write approximately 400 letters to the Royal Society.

investigations of the cell utilised the microscope to its fullest extent, however it required advances in technology before more could be elucidated.

Compound microscopes through the eighteenth and early nineteenth century were no better than good simple microscopes. They did however become more ornate and fashionable, and many nineteenth century scientists would aspire to be the owner of a microscope. However, none of the men described above had any particularly passionate pupils, leaving few (if anyone) to continue their work. Critics remained however, concerned that instruments like microscopes were making visible what God had intended to be invisible. Two such influential gentlemen of the time, philosopher John Locke (1632-1704) and physician Thomas Sydenham (1624-1689), both considered microscopical observations to be a distraction from true understanding of human health and pathologies. Physicians like Sydenham were also despondent regarding microscopy, since it had not improved diagnosis or treatment of illness (Magner, 2002). A usual framework is that through the eighteenth century, the microscope instead became more ornamental and decorative, and a novelty for the wealthy. Whilst the brass (or silver, or gold) elements of the microscope became more lavish, the lenses were more ignored, and relatively poor quality images were observed. A different potential story has come to light however, as suggested in Marian Fournier's *The Fabric of Life* (1991). Fournier instead suggests that although there was a peak in microscopical investigation between 1675 and 1710, there was a second around 1750. Fournier does not ascribe this to any significant changes in the instrumentation (agreeing with previous thought), but considers the continuing scientific revolution occurring through the eighteenth century. Despite its critics, the microscope became a useful tool for extending knowledge of natural theology and developing mechanical philosophy during this period. For Fournier, this work resulted in a more definitive theory regarding the construction of the body, such as the "intricate arrangement of vessels...thought to bring about the various physiological processes" (Fournier, 1991, p196). For Fournier, the eighteenth century was not a century of slow development for the microscope, but rather its use as a tool for something other than observing the natural history of small animals, or the magnification of everyday objects. In the mid-eighteenth century however, when there was an intellectual shift away from physical reductionism, the microscope became a popular instrument once again. The view that the invisible must be continuation of the visible was disputed and led to the use of the microscope as a tool in this debate. Eventually however, the wealthy amateurs requiring microscopes led to improvements in convenience and design. For example, microscopes were produced that would stand on a table at an appropriate height for study and drawing. It was not until the nineteenth century that microscopy began to be taken more seriously again, and improvements were made to lenses, including multiple convex lenses to improve magnification. Similarly, chromatic lenses, capable of splitting light into its different wavelengths, were also developed.

Nineteenth century use of light microscopy in biology

Developments in tool-making meant that dramatic improvements could be made to instruments (such as microscopes) in the nineteenth century. For example, in England, T. Harris produced the brass 'acorn' microscope, so-called because it was a compound microscope able to fit into one's pocket; ideal for fieldwork. Other 'exhibition' microscopes were also manufactured for teaching or demonstrations, with large stages capable of holding many specimens. Joseph Jackson Lister (1786-1869) used his knowledge and understanding of light and optics to develop compound microscopes that eradicated spherical artefacts which were often seen. Immersion is now known (and still used) to improve microscopic resolution, and was tested as early as 1812⁹. During the nineteenth century, physician Ernst Abbe (1840-1905) and the instrument maker Carl Zeiss (1816-1888) worked together to develop better microscopes, considering resolution and magnification together¹⁰. Abbe used mathematics to determine how microscopes could produce sharp images¹¹, and Zeiss created the more advanced instruments (Zeiss became the dominant microscope manufacturer of the late nineteenth century; a reputation that remains today). Phase contrast microscopy was also developed; this technique allowed the visualisation of different organelles of cells as the image produced by the microscope could differentiate between, for example, a fat globule and the nucleus. The theoretical limit of light microscopy was 500-fold magnification and a resolution of 0.2mm by the early decades of the twentieth century.

Developments in microscopy continued, as did investigation using the microscope, and by the early 1800s, various animal tissues were known, such as cartilage, bone, and muscle (For example, see Pritchard and Goring, 1847). The French physiologist Henri Dutrochet (1776-1847), after studies in animals and plants, suggested a unifying theory of tissues, claiming they were made up of small cells, varied in shape and structure¹². Dutrochet was a scholar who continued to work in isolation at his country home during the French Restoration (Pickstone, 1978). Dutrochet was made a full member of the Académie des sciences in 1831, suggesting that during his lifetime, Dutrochet's work was known and appreciated by natural scientists in France (despite his apparent reclusiveness). Dutrochet believed that both plant and animal physiology were aspects of the same discipline, which in turn was part of physics; this was discussed briefly in Dutrochet's

⁹ For example, by Sir David Brewster (1781-1868).

¹⁰ Arguably, Abbe's predecessor was the Dutch mathematician and physicist Christiaan Huygens (1629-1695), whose works on reflection and refraction were published in the late seventeenth century (Masters, 2006).

¹¹ The 'Abbe Formula' relates resolution to the aperture of the lens and the wavelength of the illumination light.

¹² It has been claimed that Dutrochet's work was actually an unacknowledged inspiration for Theodor Schwann's contribution to cell theory (for example, see Pickstone, 1978).

'corrected papers' of 1837. Although mentioned, Dutrochet's consideration of general physiology as related to physics is not developed in his work. This said, Dutrochet can generally be placed within the realms of nineteenth century French physiological studies and *sciences naturelles*. Historian of science John Pickstone suggested that physiology in France during the nineteenth century (a flourishing discipline in the first decades of the century) included Dutrochet's ideal that physiological models were applicable to both plants and animals – there were no 'ordering of functions or organisms'. It was also concerned with the action of entire organs (rather than individual tissues), and allowed chemical and physical explanations of actions (Pickstone, 1978, p52). Pickstone suggests that Dutrochet was very much a product of his time, exchanging "rational physiology" for experiment and observation, conforming to the new *biologie* and, for Dutrochet, advancement of physiology (Pickstone, 1978, p55).

The liberal materialism in post-Napoleonic France was rather different to the situation in Germany during the period; 'biology' had become more scientific, developing from natural philosophy. Dutrochet understood what is now considered to be the three notable features required for Cell Theory: theory of cellular function, unity of structure, and the appreciation on life on this scale. Why then, Pickstone asks, was Dutrochet not as influential as Theodor Schwann with regards to Cell Theory? This brings us back to the history of the light microscope.

Contemporaries Matthias Jakob Schleiden (1804-1881) and Theodor Schwann (1810-1882) are known for their work contributing to The Cell Theory. The botanist Schleiden and the zoologist Schwann both came to similar conclusions: that each cell was an independent unit, which could also function as part of tissues and organs. Schleiden, mostly concerned with observing, describing, and naming plants, suggested that plants were made entirely from 'cells', and that the plant would arise from a single cell. Schleiden's friend Schwann would then extend this theory to animals in 1839. Again, Schwann made many microscopical observations of tissues, and concluded from his work that cells were the basic units of life. Like Schleiden, Schwann conceived that all cells of a body would have arisen from a single cell. In France, the microscope generally came into use amongst scholars in the 1820s; these were poor instruments however, and this led to a downturn in the French market for the microscope, and lack of trust in French observations. The microscope was introduced into Germany during the same period, by the many young gentleman scholars drawn to Germany's strong reputation for the 'new biology'. The interest in developmental biology in Germany made the microscope an important and useful tool for research, whilst in France the few improved instruments that were in use found work with comparative anatomists. Both Schwann and Dutrochet inevitably made mistakes in their work; however, with French microscopic *biologie* mistrusted in the middle decades of the nineteenth century, and Schwann's work fitting into the framework a more gradual, large, collaborative research project, future microscopists were much more likely to consider correcting and re-interpreting Schwann's work than Dutrochet's (Pickstone, 1978).

From the late eighteenth and into the nineteenth centuries, observations were also made of structures inside cells. In 1781, Italian scholar Felice Fontana (1730-1805) described 'oval bodies with a spot' inside cells, as did German botanist and physician Franz Meyen (1804-1840) in 1826; fifty years later, Scottish botanist Robert Brown (1773-1858) (then at Oxford University) identified a similar structure in plant cells, which he called a nucleus, concluding that this was a normal element of all cells. Mitochondria were possibly first observed during the 1840s, a few years after Brown described the nucleus. However, it was the German pathologist Richard Altmann (1852-1900) who first described the structures he called 'bioblasts' in 1890. Altmann concluded that these bioblasts were actually "elementary organisms" living inside cells; the symbiotic nature of mitochondria would not be recalled until 1970. The Italian physician Camillo Golgi (1843-1926) was the first to describe the Golgi apparatus in 1897 (which was named after him a year later). Also during this period, questions were being asked with regards to the functions of these organelles, including cell division. The division of pre-existing cells were observed in three fields of research in particular: the division of protists, filamentous algae, and the cleavage of eggs. Both the German physician and pathologist Rudolf Virchow (1821-1902) and Polish German physiologist and embryologist Robert Remak (1815-1865) made generalisations about cell division being the standard method for multiplication during the 1850s (Baker, 1953).

The microscope became an essential instrument for studying development in the late nineteenth century. Already popular in Germany, much work was carried out utilising the microscope and a variety of animals. For example, in 1878, German biologist Walther Flemming (1843-1905) observed and described mitosis in the salamander *Triturus maculosa* (Cunningham, 1882). These descriptions were published in Flemming's text *Zellsubstanz, Kern und Zelltheilung* [Cell Substance, Nucleus and Cell Division], where Flemming expanded on Cell Theory by stating that not only did all cells arise from other cells, but that nuclei did as well: '*omnis nucleus e nucleo*'. The German embryologists Hans Driesch (1867-1941) and Wilhelm Roux (1850-1924) were at the forefront of this research, Roux referring to his work as *Entwicklungsmechanik* (developmental mechanics). In the late 1880s, Roux began 'pricking experiments' using two-cell frog (*Rana esculenta*) embryos. Using a fine, hot needle, Roux would puncture one of the cells (with the aim of killing it, and no longer able to contribute to development), whilst leaving the second cell to develop normally. Roux observed that the usual result of the experiment was that half an embryo would develop from the cell left intact. Therefore, Roux argued, the material for development of one half of the embryo was contained in one of the cells at the two-cell stage. Later (during the 1890s), Roux decided that since the remaining half appeared to be developing normally, there is no need for the second half of the egg. The 'causal topographical conception', as Roux called it, stated that as long as the living half of the fertilised egg had all of the conditions required to develop (e.g. oxygen, heat, etc.), the remaining half could continue its development normally (Spemann, 1938, p19-20).

None of the work carried out in Europe (and particularly in Germany) through this period would have been possible without continued use and development of the light microscope. The company of Carl Zeiss ('Carl Zeiss Jena'; now 'Carl Zeiss AG') in Jena, Germany, began by creating large aperture microscopes. This was a useful interpretation in the design of compound microscopy, since it would allow bright images to be created. With the demand for many high quality microscopes throughout Germany during the nineteenth century, Zeiss' business did particularly well, selling more than a thousand microscopes within eighteen years. After Zeiss met with Abbe, August Köhler (1866-1948), and Otto Schott (1851-1935), a glass chemist, the men collaborated and created what was arguably the highest performing microscope available in the late nineteenth century. This included the development of parfocal lenses, allowing the user to switch objectives whilst retaining focus. As well as Abbe, Zeiss employed other scientists, including Köhler. The German zoologist and physicist is now known for the Köhler illumination system. This system allowed Zeiss microscopes to project light uniformly from the specimen (whilst the resolution is retained); even today, commercial light microscopes are all designed with Köhler illumination in mind. Also early in the Carl Zeiss Jena history, Richard Zsigmondy (1865-1929) and Henry Siebentopf (1872-1940) developed ultramicroscopy in 1903¹³. This was a type of dark-field microscopy (based on the scattering of light, not reflection), which used a bright illumination source; although it allowed detection of smaller particles than the optical microscope, there were issues with resolution.

Demonstrating the popularity of the microscope for scholars, the first microscopical societies were founded. The Microscopical Society of London was, at first, a meeting of seventeen gentlemen at Wellclose Square, London, on 3rd September 1839. These gentlemen, including Joseph Lister, met "to take into consideration the propriety of forming a society for the promotion of microscopical investigation, and for the introduction and improvement of the microscope as a scientific instrument" (Royal Microscopical Society, 2014). A further provisional meeting was held on 20th December 1839, and the first meeting of the Society was held on 29th January 1840 in the Horticultural Society's rooms at 21 Regent Street. Professor Richard Owen was elected President, and announced that there were 139 original members. Early meetings, documented in some detail in *The American Journal of Science and Arts*, included papers on the examination of teeth, the development of plant vasculature, and methods for the best mounting of microscopes. Members also brought along exhibits for others to observe under microscopes set-up on tables for the meetings. The Society swiftly organised a journal, *The Microscopic Journal & Structures Record*, first published in January 1841. This was preceded by *Transactions of the Microscopical Society* a year later. An 1844 report proclaims the success of the Society, and, despite a membership fee of just one guinea a year, all expenses have been paid and the Society procured three microscopes (The Microscopical Society of London, 1844). In 1866, the Society council applied for a Royal

¹³ Zsigmondy won the Nobel Prize in Chemistry in 1925 for his work on colloids, greatly aided by his development of the ultramicroscope.

Charter of Corporation, which was granted. On 1st November 1866, the Society changed its name to the Royal Microscopical Society.

Swift developments in twentieth century microscopy and cell culture

In the first few decades of the twentieth century, it became possible to isolate and culture pure strains of cells. Much could be learned about these cells *in vitro*, greatly improved by the development of phase-contrast microscopy, microcinematography, and vital staining. Cytochemistry was also aided through the twentieth century by use of the light microscope. Techniques were developed to allow visualisation of enzyme reactions, and eventually, electron microscopy would allow the study of reaction localisation.

In the formative years of the twentieth century, the first techniques were developed that would keep cells alive outside of a body. Initially, embryonic tissues would grow better than adult tissues, which seemed relatively inactive. One such initial technique was to extract tissue from a chick embryo, place it in a clean glass dish, and cover with a sort of nutrient medium, such as blood serum. After a few days, cells could be seen emerging from the explant, and as more was learned about cell types, each could be distinguished from one another under the light microscope. Successful, useful, cell culture then clearly required light microscopy. Early work was focused on coaxing cells to survive *ex vivo*, however once this had been established, cell culture became an important technique for learning about cellular differentiation, function, and behaviour. Through the twentieth century, significant improvements continued to be made in standardising cell and tissue culture, including the development of various media and isolation and culture of individual cell types. Whereas Germany was at the forefront of biology (in particular developmental biology) at the end of the nineteenth century, cell biology was a discipline developed in England (particularly at the Cambridge Research Hospital, later the Strangeways Research Laboratory), and, to an extent, in the USA¹⁴. Prior to the outbreak of the First World War, many Eastern European researchers moved further into Western Europe and the USA to continue their work. The dominance of German biology now became a dominance in British and American biology, and resulted in a change of publication language; up until the beginning of the twentieth century, much that was published in respected journals was in German. With the movement of scientists to English-speaking countries, English became the prevailing language of biology. Just as a social change led to a shift in publication language, cell biologists drew on their understanding of Western society to help them understand cells and tissues. As functioning society required each individual to have their role (the baker, the cobbler,

¹⁴ This was achieved mostly through the efforts of the French surgeon and biologist Alexis Carrel (1873-1944), who emigrated to the USA around the age of 30.

the magistrate), the same was considered true for the organism¹⁵. The success of tissue culture warped the view of the organism; bodies could be considered as a stack of tissues that could be removed and reformed elsewhere – potentially immortal¹⁶.

Not everyone was immediately impressed by the new technique however. Biochemist Erwin Chargaff (1905-2002) suggested that tissue culture could be a "slippery slope to social disaster" (Andrews and Nelkin, 1998, p54), whilst physiologist Jacques Loeb (1859-1924) saw the method as an opportunity to learn about the "technology of living substance" (Pauly, 1987, p51). Philip White (of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine) claimed cell culture was heralded as a revolutionary technique (see White, 1955); having failed to greatly further understanding of body structure and function, some believed that tissue culture technique had therefore failed. Concerned that this might stop younger researchers from taking up the method, White wrote to highlight the achievements cell culture had aided. White observed that by the mid-1950s, there were many cell culture techniques available to study cells, which could be cultured in highly controlled environments. At the time, hanging drop cultures¹⁷ and flask cultures were the most frequently used techniques, however White highlighted the use of tissue culture as well.

"There is hardly a branch of science dealing with the cellular biology of higher animals and plants which has not profited in the last few decades from some sort of "tissue culture" study" (White, 1955, p364).

Light microscopy remained the best way to view living cells. Since living cells are almost transparent, it was difficult to see tissue or cell structure using only the light microscope. This led to the development of dyes, or stains, which would colour certain cellular structures after fixation. Although early fixation techniques would make proteins in the cell coagulate, certain organelles, such a mitochondria, would retain their original shape. These so-called 'vital stains' could be used on living cells without killing them. In addition, fluorescence microscopy was developed through

¹⁵ In his volume on tissue and cell culture, physiologist Edward Willmer actually compares cell culture to the Great Depression of the 1930s; high numbers of unemployed people led to unprecedented shifts in society. Willmer believed that this was similar to the uprooting of tissues from the organised organism, and attempting to nurture them in an unknown situation (that of the laboratory) (Willmer, 1935).

¹⁶ For example, Alexis Carrel's 'old strain' of chick embryo cells appeared to continue growing indefinitely, lasting many decades and outliving Carrel himself (Wilson, 2011).

¹⁷ This is a method of cell culture that consists of a small drop of media (or plasma), suspended from a watch glass. The drop remains hanging due to gravity and surface tension, and allows cells to grow in three-dimensions (as opposed to two, as with conventional cell culture).

the nineteenth and twentieth centuries. Fluorescence was first documented by Scottish physicist David Brewster (1781-1868), and capitalised on by University of Cambridge professor of mathematics George G. Stokes (1819-1903). In 1852, Stokes published a paper describing the changes of wavelengths of light. This change became known as the 'Stokes shift'. The phenomena of autofluorescence was described by Hans Stübel, in 1911; Stübel suggested that autofluorescence could be used as a diagnostic tool. With this in mind, the first fluorescence microscopes were developed over the next few years, by a team at Zeiss, and another team at a different German company, Reichert. Both microscopes used carbon arc lamps. In 1914, Stanislav Von Prowazek (1875-1915), a Czech zoologist, used fluorescent dyes to observe living cells under the fluorescence microscope; it was almost three decades later however that the American physician and pathologist Albert Coons (1912-1978) first coupled fluorescein isocyanate with antibodies. This "putting tail lights on antibodies", as Coon referred to it, soon became the established technique of immunofluorescence, one of the most significant methods used in cell biology today (Karnovsky, 1979).

During the twentieth century, the complexity of microscopes greatly increased, and even the humble light microscope was modified to allow ever-clearer views of the invisible. The concept of photomicroscopy was developed relatively early on in the history of microscopy, with Thomas Wedgwood (1771-1805) proposing that microscope images could be copied onto 'prepared paper'¹⁸. Many other scholars interested in microscopy and photography would attempt to create photomicrographs over the following hundred years. The first photomicroscopes however were probably made by a company named Leitz. Leitz built a vertical photomicroscope in 1886, created based on the designs of the company's founder, Ludwig Leitz (1867-1898). Development of designs resulted in the 1933 introduction of the 'Panphot' microscope, which included a microscope with a rigid vertical stand for a camera. Leitz continued its dominance in photomicroscopes into the middle of the twentieth century (other companies, such as Zeiss, also went through a similar arc of developing photomicroscopes). Throughout the early part of the twentieth century, photography equipment and technique would also improve, affecting the results of photomicroscopy. The relatively simple set-up and the generally good results meant that photomicroscopy became an important data collection technique for cell biology and allied disciplines.

The next step of course was microcinematography. Microcinematography was first developed in France. University teacher Julius Ries created time-lapse films of embryonic development in 1907; thinking his students would not believe that all cells could develop from only other cells, Ries created time-lapse films of sea urchin development, reducing a fourteen hour process to two minutes of film. For Reis, such films were preferable to drawings and images of

¹⁸ It is likely however that the article was not widely read, but chemist Humphrey Davy's (1778-1829) knowledge of Wedgwood's idea could have aided in popularising it (Davy, 1802).

fixed sections, since it was an opportunity to view living, moving cells (Landecker, 2009). French biologists Jean Comandon (1877-1970) and Justin Jolly (1870-1953) were also two of the first to make films of cells under the microscope. In 1913 and 1914, Comandon and Jolly made films focused on cell division, wanting to demonstrate the continuous process (and were particularly interested in the action of chromatin)¹⁹. This technique allowed a shift in the perception of cells viewed using microscopy. The histological stains (for example, those developed by German immunologist Paul Ehrlich [1854-1915]) allowed visualisation of cellular structures that were incomprehensible using only bright-field microscopy. Initially considered a strength, as knowledge was created based on these new findings, fixing and staining became considered a hindrance. Research focus shifted from morphological studies to functional analysis at the beginning of the twentieth century, and researchers needed to see and record living cells and tissue (Landecker, 2009). Coupled with film cameras and phase contrast microscopy, live cell imaging became less complex and expensive, and produced good results. It became standard practice for cell biologists in the latter half of the twentieth century.

The phase contrast microscope was also a significant development in twentieth century, borne of the integration of light polarisation and interference with microscopy. University of Groningen Professor of Theoretical Physics, Frits Zernike (1888-1966) claimed that his interest in light diffraction began in 1920. Zernike observed optical path issues with unavoidable, minute imperfections on diffraction grating. A decade later, Zernike's laboratory obtained a large enough piece of concaved grating that Zernike attempted to focus on using a small telescope; however, the stripy image created would no longer be clear when the small telescope was focused on the grating – a peculiar phenomenon that Zernike could not initially explain (Zernike, 1955). Further work led to the development of phase contrast microscopy, in which there is a phase shift in light as it passes through a transparent specimen; initially, Zernike claims he was inspired by the earlier work of Abbe (Zernike, 1955). This changed the brightness of the image produced depending on the density of the specimen (i.e., a method that does not use light absorption, as previous microscopes had, but interference). In cell biology, this development was particularly important; cells are transparent objects that are often difficult to distinguish clearly using bright field microscopy. Using phase contrast microscopy, larger cellular structures could be identified with relative ease. In 1932, Zernike took his work-in-progress to Carl Zeiss Jena; the scientific associates, Zernike claims, were rather unenthusiastic. Ironically, Zernike believed that the work of Abbe, linked with the Zeiss company until his death in 1906, was considered the ultimate authority in microscope technology, and the scientific associates even twenty-five years later did not see that Abbe's work could be improved on. Refining his design, Zernike returned to Zeiss, who developed his instrument. Although this development was delayed due to the outbreak of the

¹⁹ Hannah Landecker (2009) suggests that Comandon and Jolly's use of microcinematography was not only useful for demonstrating the role of chromatin in cell division, but also to remind biologists that they were dealing with living entities.

Second World War, Zeiss were able to market the phase contrast objectives and accessories in 1941 (Zernike, 1955). For his demonstration of the phase contrast method, and especially for the development of the microscope, Zernike was awarded The Nobel Prize in Physics for 1953. Two years after Zernike's Nobel Prize was awarded, Polish physicist Georges Nomarski (1919-1997) published his work detailing the theory for another interference-based microscope: differential interference contrast (DIC) microscopy. As with phase contrast, DIC microscopy enhanced the contrast of transparent specimens, but removed the diffraction halo typical of phase contrast images (Masters, 2006; Murphy and Davidson, 2013).

One of the more recent microscopy developments is the electron microscope, developed in the mid-twentieth century. Nicolas Rasmussen (1997) claims that the electron microscope evolved out of research developing cathode-ray technologies (in particular the oscillograph); improved technologies allowing better vacuums and electronic tubes, alongside Louis de Broglie's (1892-1987) matter wave theory²⁰, made the 1930s the ideal time for development of the electron microscope. The first to begin development were the physicist Ernst Ruska (1906-1988) and engineer Max Knoll (1897-1969) in Berlin in 1930, and a prototype was created in 1931. By 1933, this was demonstrated to surpass the resolution of the light microscope. Independent projects soon started elsewhere however, including Canada, Britain, Holland, Sweden, America, France, and Belgium. The company Siemens-Schuckertwerke obtained the patent for an electron microscope in 1931.

In 1937, Helmut Ruska (1908-1973) joined his brother to help develop the electron microscope for use in the biological sciences. Although advances in biological sciences were a principle aim of those developing electron microscopy, there were foreseeable problems with this technique that were unproblematic for light microscopy. In particular, there was an issue with specimens; the vacuum required prevents any live cell imaging. Specimens also required fixing (dehydrating) carefully to prevent distortion of proteins and organelles, whilst needing to be sliced very thinly. These drawbacks were overcome by the determined however. One of the first laboratories in the USA to possess an electron microscope was the Interchemical Laboratory in New York; in collaboration with the Rockefeller University's Albert Claude (1899-1983), one of the first cell biologists, the first electron micrograph of an intact cell was created in 1945²¹. Meanwhile however, German applied physicist Manfred von Ardenne (1907-1997) created the scanning electron microscope (SEM). Ardenne's microscope was far more useful in biological sciences, since with the SEM, specimens can be viewed in wet conditions, within a low vacuum, and at a range of

²⁰ de Broglie's wave-particle duality theory (also known as the de Broglie hypothesis) concluded that concepts applied to optics could also be applied to electrons. de Broglie won the Nobel Prize for Physics for this account in 1929.

²¹ So important was this image, that Nobel Prize winner (and colleague of Claude) George E. Palade (1912-2008) announced that it was the 'birth certificate' of the cell biology discipline (The Rockefeller University, n.d.).

temperatures. The SEM was developed by several groups over the next few decades, with the first commercial SEM available for laboratories in 1965. The availability of such an instrument revolutionised cell biology in the latter half of the twentieth century (see, for example, Rasmussen, 1997; The Rockefeller University, n.d.; Masters, 2006).

Microscopy: the black box of modern cell biology

The black box was a theory developed in mid-twentieth century sociology of science, particularly as part of the actor-network theory (devised by sociologist Michel Callon and philosopher Bruno Latour in the early 1980s). The black box theory suggests that there is an input and an output, and between them is a 'black box'; we do not know the functions of the black box, nor how it works (although we can gather some understanding of the process from the input and output). Ihde (1990) uses phenomenology to consider the relationship people have with technology; one of Ihde's four human/technology relationships is referred to as *background* relations, such as central heating. The central heating system is a 'black box': it functions with an input (such as turning it on), and an output (heat), although most people are unaware of exactly how this system works. For most individuals then, this is a black box (Bunge, 1963; Ihde, 1990; Introna, 2011).

Through the last few centuries, technology and scientific research have become more entangled, with each now reliant on the other; biology has been no exception. For example, the expansion of the observable has increased significantly over the past hundred years, with more refined microscopes becoming available. Researchers are now expected to have mastered many techniques, including the use of complex apparatus, to create the data required to publish²². However, the complexity of such techniques and instruments mean that fewer and fewer biologists have a detailed understanding of the tools they are utilising. Whilst physicists for example may be more interested in the mechanics of their apparatus, biologists now are less so, simply using these machines as tools²³. Instead, biologists are now encouraged to use "complicated 'black boxes' that produce the results they need" (Nature, 2007, p116). I propose that the light microscope (and its variants) have become one such 'black box'. One obvious piece of evidence for this is the lack of methodological detail required regarding microscopy techniques

²² In cell biology, this can include knowledge and understanding of biochemistry, physiology, genomics, proteomics, cell culture, and microscopy techniques, for example.

²³ This is a more recent phenomenon; up until the latter decades of the twentieth century, biologists would be more concerned with the equipment they were using, often spending time designing and creating unique tools or apparatus (such as fine glass pipettes for individual cell manipulation). Arguably, standardisation of biology, potentially necessary for extrapolation, accurate replication of studies, and general progress of science, has reduced many biological techniques and methods to black boxes.

in published papers. For instance, many cell biology papers would have had significant cell culture work attached to them, however at no point is the use of bright-field or phase-contrast microscopy mentioned; I suggest that this is because it is now part of the 'cell culture black box' - cell culture, although now well-understood, is carried out by researchers (particularly in the younger generations) who perhaps have little appreciation for the precise mixture of ingredients in a standard bottle of media, how the flow cupboard functions to keep a working space sterile, or how the light microscope in the tissue culture room works²⁴. In fact the reason cell culture has actually become so common, White claimed, was that its methods generally so overlooked, despite many disciplines being linked by a requirement to keep cells, tissues or organs alive *ex vivo* (White, 1955). In addition, more sophisticated microscopes (such as confocal or electron) are also used frequently in cell biology research, however, again, few details are given in publications, and it is possible that researchers simply follow instructions and push buttons in order to generate the data required.

Conclusions

The microscope was first proposed following the development of eyeglasses in early modern Europe. Those skilled in creating glass lenses and scientific instruments found themselves capable of creating early simple or compound microscopes, which initially appeared to function (to an extent) as a curiosity. This is demonstrated in Hooke's *Micrographia*; scholars and other wealthy interested persons could use these new instruments to extend their visual world, almost randomly placing objects under the microscope to examine what could not be seen previously. As scholarly endeavours proceeded from natural philosophy, to natural history, and eventually what we would now recognise as biology, the microscope became an increasingly useful tool. As investigations continued into the minutiae of small organisms, and as various tissues extracted from animals and plants continued to fascinate, comparisons were drawn. What was understood from the normal visual world was extrapolated to the newly visible. Clear differences in biology were established by the use of reliable instruments (such as those between France and Germany in the nineteenth century) –

²⁴ There is however another reason that methods and materials are described so sparsely in research articles: the lack of space. Often, there is little room available for details in publications, and so the most important aspects of protocols, or variations from a standard protocol, are given priority. Although this goes some way to explain why so little is mentioned in research articles referring to standard microscopy techniques (for tissue culture), this, I believe, enhances the status of microscopy as a black box. Since other researchers do not necessarily need to know the intricacies of microscopy procedures to repeat experiments and obtain the same results, there is no motivation for researchers to include such information.

demonstrating the importance of microscopy to several developing biological disciplines. The status of the microscope has not changed; De Robertis, Nowinski, and Saez (1970) suggest that cell biology of the twentieth century has two main reasons for its swift advancement. The first is its usefulness in other areas of biological sciences (such as genetics and biochemistry). Secondly, due to the swift advances in microscopy (including electron microscopy).

Cell culture became important through the twentieth century (for example, see Wilson, 2011, and Landecker, 2010). From small explant cultures, to Carrel's 'old strain', isolation and culture of single cell types, to development of specific cell lines, noteworthy advances have been made in the twentieth century with regards to cell culture and its techniques. Standardisation of media and consumables, and availability of multiple cell types has ensured that cell culture now has a useful role in several aspects of biology; likewise, cell biologists are now expected to work across several disciplines and have working knowledge and understanding of these. I suggest that this is one reason why the basic light microscope has become a black box in cell biology, and in particular its role in cell culture. The role of both cell culture and microscopy has changed over the past hundred years; the uses of the microscope have extended to include photomicroscopy and live cell imaging. No longer are microscopes interesting enough regardless of which specimens are being observed. The role of the light microscope has changed from an object of curiosity to a mundane tool. Similarly, cell culture began as experimental – it was exciting to work towards growing cells *ex vivo*. Once this had been accomplished, new roles were needed for the technique, and cell culture became a useful way of studying cell division, differentiation, motility, morphology etc.; like the microscope, the curious *ex vivo* cell cultures became mundane tools. Routine laboratory cell culture work became 'gardening': seeding, feeding, propagating, splitting. In the latter decades of the twentieth century, cell culture itself (including the microscopy element) became a black box; some researchers are only now going back to standard cell culture techniques, although with a very specific aim: the creation of stem cells from somatic cells (see, for example, Takahashi and Yamanaka, 2006; Obokata *et al.*, 2014). The complex physics of microscopy however remains a black box for most biologists, suggesting that researchers should carefully consider methodologies, techniques, and equipment used to fully understand and appreciate results presented.

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